## REMARKS

The Office Action mailed October 20, 2006, has been received and reviewed. Claim 7 is cancelled herein. Claims 1 and 10 have been amended herein. New claim 24 is presented herein. Claims 3, 6, 8, 9, 13-15, and 23 have been withdrawn from consideration. All amendments and claim cancellations are made without prejudice or disclaimer. Applicants respectfully request reconsideration of the application.

### Priority

The Examiner has requested that applicants provided a certified copy of the priority document. Applicants note that a certified copy of the priority document has been provided to the Office.

### Drawings

The Examiner has objected to FIGs. 3A and 3B as they appear to be a continuation of the same figure. The Examiner suggests it would be remedial to "remove the references to parts A and B. Office Action mailed October 20, 2006, at page 3. Applicants note that 37 C.F.R. § 1.84(u)(1) provides that "[p]artial views intended to form one complete view, on one or several sheets, must be identified by the same number followed by a capital letter." Applicants thus submit that the labeling FIGs. 3A and 3B is in accordance with the rules. However, applicants have amended ¶ 22 of the Specification to clearly indicate that FIG. 3B is a continuation of the view presented in FIG. 3A. Consequently, applicants respectfully submit that the amendment to the specification overcomes the Examiner's objections.

### Specification

The Examiner has objected to ¶¶ 20, 30, 35, and 43 of the Specification as containing browser executable code. Applicants note that appropriate correction has been made herein.

### Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1, 2, 3, 4, 7, 11, 12, and 16-21 stand rejected under35 U.S.C. § 112, second

paragraph, as assertedly being indefinite. Specifically, it was thought that claim 1 was vague and indefinite for the recitation of "in a eukaryote with a preference for non-homolgous recombination." Office Action mailed October 20, 2006, at page 4. The Examiner notes that certain yeast cells have a preference for homologous recombination. *Id.* at page 5. The Examiner further notes that claim 10 limits the eukaryotic cell of claim 1 to yeast. *Id.* The Examiner thus concludes that claims 1 and 10 are inconsistent, and thus indefinite as it is asserted that certain yeast cells, which prefer homologous recombination, cannot be the eukaryote with a preference for non-homolgous recombination of claim 1. *Id.*

It was further thought that both claims 1 and 7 were vague and indefinite as the nucleic acid recited in the respective preambles was not used in any of the positive action method steps. *Id.* at page 6. Applicants note that the rejection of claim 7 is moot as claim 7 has been cancelled herein. Applicants respectfully traverse the remaining rejections as hereinafter set forth.

Regarding claim 1, applicants respectfully submit that the recitation of "in a eukaryote with a preference for non-homolgous recombination," in claim 1, in combination with the recitation of "yeast" in claim 10, does not make claim 1 indefinite. Applicants note that one of skill in the art would understand that there are yeast that have a preference for non-homologous recombination; thus claim 1 is not indefinite. However, in the interest of expediting prosecution, applicants have amended claim 10 so as to no longer recite "yeast," thus mooting the rejection. Consequently, applicants respectfully submit that claim 1 can no longer be considered indefinite for the recitation of "yeast" in claim 10. As such, applicants respectfully request the withdrawal of the rejection of claim 1 under 35 U.S.C. § 112, second paragraph and reconsideration of same.

Claim 1 was further considered indefinite as "there are no claims positive action method steps that require a nucleic acid." Office Action mailed October 10, 2006, at page 5. Although the applicants do not agree that any of the claims are indefinite, in order to expedite prosecution, claim 1 has been amended herein. Claim 1, as amended, recites "providing said nucleic acid to said eukaryote." As such, applicants respectfully submit that claim 1 can no longer be considered indefinite for the failure recite a positive action method step that requires a nucleic acid. Consequently, applicants respectfully request the withdrawal of the rejection of claim 1 under 35 U.S.C. § 112, second paragraph, and reconsideration of same.

In addition, applicants respectfully submit that claims 2, 3, 4, 11, 12, and 16-21 are definite, *inter alia*, as depending, directly or indirectly, from definite independent claim 1. As such, applicants respectfully request the withdrawal of the rejections of claims 2, 3, 4, 11, 12, and 16-21 under 35 U.S.C. § 112, second paragraph, and reconsideration of same.

**Rejections under 35 U.S.C. § 112, First Paragraph**

Claims 1, 2, 4, 5, 7, 10-12, and 16-21 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly lacking enablement. Specifically, regarding claims 1, 2, 4, 5, 10-12, and 16-21, it was thought that the Specification "does not reasonably provide enablement to steer an integration pathway towards homologous recombination in a eukaryotic cell *in vivo* and does not provide enablement for transient inhibition of integration via nonhomologous recombination by providing a mutant component involved in nonhomologous recombination." Applicants note that the rejection of claim 7 has been mooted by the cancellation of claim 7 herein. Applicants respectfully traverse the remaining rejections as herein after set forth.

The Examiner, in reviewing the Wands factors for enablement, cites several factors to which she applies the following reasoning. In "nature of the invention," the Examiner asserts that "the preamble of independent claim 1 reads on the integration of a nucleic acid of interest into a eukaryotic cell *in vitro* or *in vivo* (i.e. gene therapy)." As a first matter, applicants note that, as a general rule, items recited in the preamble do not determine the scope of a claim. *See, e.g.*, M.P.E.P. § 2111.02.

Further, applicants respectfully assert that the Examiner's characterization of *in vitro* or *in vivo* as requiring "gene therapy" is flawed. Applicants note that there are many single cell eukaryotic organisms that prefer nonhomologous recombination that can be grown in culture. Subjecting these cells to the methods of the present invention would be considered, by one of ordinary skill in the art, as occurring *in vivo*, as these cells only exist in a single cellular format. Thus, the inserting a nucleic acid of interest into another nucleic acid does not require "gene therapy." Moreover, applicants respectfully submit that the claims are not specifically directed to "gene therapy", but are directed to methods of introducing nucleic acids into other nucleic acids via homologous recombination. As the claims not specifically directed to "gene therapy," or any

therapeutic effect, applicants respectfully submit that they are not required to enable the use of the claimed methods for the purposes of gene therapy.

Regarding "breadth of the claims," the Examiner alleges that "the claims encompass the use of the claimed method in any eukaryotic cell of any organism." Applicants note that this interpretation is overly broad as the claims are directed to eukaryotes with a preference for non-homologous recombination.

In the Examiner's remarks regarding "state of the art," the comments are limited to the state of the art for gene therapy. As noted *supra*, methods for integrating nucleic acids are being claimed, and the claims are not specifically directed to gene therapy.

Regarding "guidance of the specification and existence of working examples," the Examiner asserts that "the specification envisions the treatment of cancer and genetic diseases." Office Action mailed October 20, 2006, at page 8. While the Specification may envision broad applicability for the invention, applicants respectfully assert that the claims are not specficially directed to the treatment of cancer and/or genetic diseases. Consequently, applicants submit that they are not required to provide examples or guidance on enabling one of skill in the art to treat cancer or genetic diseases *per se* using the presently claimed methods.

Regarding "predictability of the art and amount of experimentation necessary," applicants note that several reports have been published in the literature, showing that integration according to the present invention is generally applicable in eukaryotes. Enclosed are publications of Takahashi, T. et al. (Mol. Gen. Genomics, 2006), da Silva Ferreira, M.E. et al. (Eukaryotic cell, 2006, 5:207-11), Nayak, T. et al. (Genetics, 2006, 172:1557-66), Krappmann, S. et al. (Eukaryotic Cell, 2006, 5:212-5), and Ninomiya, Y. et al. (Proc. Natl. Acad. Sci. USA, 2004, 101:12248-53) showing integration by homologous recombination in several species of *Aspergillus* and *Neurospora*, which are eukaryotic organisms that have a preference for non-homologous recombination. Consequently, applicants submit that the outcome of the methods claimed is predictable and reproducible over numerous eukaryotic organisms that have a preference for non-homologous recombination. In addition, it seems that great quantities of experimentation are not required as five separate laboratories were able to perform essentially the claimed techniques.

Applicants further submit that the mere fact that any experimentation may be difficult and/or time consuming does not mandate a conclusion that such experimentation is to be considered 'undue' in this art. *See, e.g., Falkner v. Inglis*, 448 F.3d 1357 (Fed.Cir. 2006); M.P.E.P. § 2164.01. Applicants submit that great expenditures of time and effort are ordinary in the field of molecular biology. As such, applicants assert that although a certain amount of experimentation may be required, such experimentation is not undue in the area of molecular biology.

For the foregoing reasons, applicants respectfully submit that claim 1 is enabled by the specification and the prior art. Consequently, applicants respectfully request the withdrawal of the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, and reconsideration of same.

In addition, applicants respectfully submit that claims 2, 4, 5, 10-12, and 16-21 are enabled, *inter alia*, as depending, directly or indirectly, from enabled independent base claim 1. As such, applicants respectfully request the withdrawal of the rejections of claims 2, 4, 5, 10-12, and 16-21 under 35 U.S.C. § 112, first paragraph, and reconsideration of same.

**Rejections Under 35 U.S.C. § 102**

Jackson

Claims 1, 2, 4, 10, 12, and 20 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Jackson *et al.* (WO 98/30902 A1) (hereinafter "Jackson"). Applicants respectfully traverse the rejections as hereinafter set forth.

Applicants note that "a claim is only anticipated if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Applicants respectfully assert that claims 1, 2, 4, 10, 12, and 20 cannot be anticipated by Jackson as Jackson does not teach each and every element of the claims.

Jackson indicates that "two ways exist for repairing DNA doublestranded breaks (DSBs). One is through the process of illegitimate recombination (also known as DNA non-homologous end-joining or NHEJ) and this is catalyzed by the KADR system now known to involve XRCC4

and DNA ligase IV. The other system is the process of homologous recombination, whereby the damaged DNA molecule exchanges information with an undamaged homologous partner DNA molecule. In mammalian cells, the illegitimate pathway tends to predominate." Jackson, at page 8, line 29 through page 9, line 5.

However, DSB repair, exemplified in Jackson by repair of a extra-chromosomal plasmid, is not the same as integration of introduced DNA into the host chromosome. Therefore, although Jackson, at page 9, lines 6 and 7, describes that inhibiting the KADR system will make the non-genomic proportion of DSBs repaired by homologous recombination increase, this does not teach or suggest that a shift in the ratio of DSBs repaired by homologous recombination actually leads to "steering an integration pathway towards homologous recombination".

Moreover, although Jackson describes that inactivation of *lig4* has no detectable effect on DNA integration via homologous recombination, it does not show that the effect of the *lig4* mutation on DNA integration via nonhomologous recombination. Therefore, in contrast to the present claims, Jackson does not teach steering an integration pathway towards homologous recombination, in a eukaryote with a preference for non-homologous recombination (comprising providing a mutant of a component involved in non-homologous recombination).

In view of the foregoing, applicants respectfully request the withdrawal of the rejections of claims 1, 2, 4, 10, 12, and 20 under 35 U.S.C. § 102(b) in view of Jackson and reconsideration of same.

Liang

Claims 1, 2, 5, and 17-21 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Liang *et al.* (PNAS, Vol. 93, pgs. 8929-8933, 1996) (hereinafter "Liang"). Applicants respectfully traverse the rejections as hereinafter set forth.

Liang describes that repair of a chromosomal double strand break via end-joining is impaired in KU80-deficient hamster cells. In addition, Liang describes that a double strand break induced at a defective Neo gene by the endonuclease I-SceI is necessary to obtain repair of this gene by an introduced neo construct, both in wildtype and ku80 mutant CHO cells. No targeted integration events are obtained in the absence of the I-SceI endonuclease. Thus, Liang

needs the presence of a I-SceI induced double-strand break in combination with a mutant in NHR to obtain efficient targeted DNA integration. Liang fails to teach each and every element of the claim as Laing fails to describe "steering an integration pathway towards homologous recombination." Liang proposes creating a new pathway for recombination via providing the I-SceI endonuclease. As such, Liang does not steer an integration pathway as required by claim 1. Consequently, applicants respectfully request the withdrawal of the rejections of claims 1, 2, 5, and 17-21 under 35 U.S.C. § 102(b) in view of Liang and reconsideration of same.

Tsukamoto

Claims 1, 2, 7, and 10 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Tsukamoto *et al.* (Genetics, Vol. 142, pgs 283-291, Feb. 1996)) (hereinafter "Tsukamoto"). Applicants note that the rejection of claim 7 is moot as claim 7 has been cancelled herein. Applicants respectfully traverse the remaining rejections as hereinafter set forth.

Tsukamoto describes the effects of mutations in genes belonging to the *RAD52* epistasis group on the repair of a plasmid via IR. Thus, Tsukamoto describes plasmid repair via IR in different yeast mutant strains. However, plasmid repair via IR occurs extra-chromosomally by a process that is not at all comparable to the process of DNA integration, which involves incorporation of newly introduced DNA into the eukaryotic chromatin structure. Moreover, Tsukamoto does not describe a method to direct integration of a nucleic acid to a predetermined site in the chromosome. Thus, Tsukamoto does not teach or suggest steering of an integration pathway as disclosed by the present invention. Consequently, applicants respectfully request the withdrawal of the rejections of claims 1, 2, and 10 under 35 U.S.C. § 102(b) in view of Tsukamoto and reconsideration of same.

Moore

Claims 1, 2, 7, and 10 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Moore *et al.* (Molecular and Cellular Biology, Vol. 16, No. 5, pgs. 2164-2173, May 1996) (hereinafter "Moore"). Applicants note that the rejection of claim 7 is moot as claim

7 has been cancelled herein. Applicants respectfully traverse the remaining rejections as hereinafter set forth.

Moore describes the repair of an HO endonuclease induced double stranded break in chromosomal DNA of wild type and *rad* mutant yeast strains. However, Moore does not teach "directing integration of a nucleic acid of interest to a predetermined site, wherein said nucleic acid has homology at or around said predetermined site", and therefore Moore cannot anticipate claims 1, 2, and 10. Consequently, applicants respectfully request the withdrawal of the rejections of claims 1, 2, and 10 under 35 U.S.C. § 102(b) in view of Moore and reconsideration of same.

**Rejections under 35 U.S.C. § 103**

Claims 5, 11, 16, and 21 stand rejected under 35 U.S.C. § 103(a) as assertedly being obvious over Jackson in view of Bundock *et al.* (The EMBO Journal, Vol. 14, No. 13, pgs 3206-3214, 1995) (Hereinafter "Bundock"). Applicants respectfully traverse the rejections as hereinafter set forth.

The teachings of Jackson are as discussed *supra*. Bundock describes the results of studies of trans-kingdom T-DNA transfer from *Agrobacterium tumefaciens* to *Saccharomyces cerevisiae*. Earlier studies showed that the T-DNA of *A. tumefaciens* is normally integrated in plants via the IR process. Bundock describes that T-DNA of *A. tumefaciens* is integrated via the HR process in the lower eukaryote *S. cerevisiae*. The authors conclude that host factors (in this case of *S. cerevisiae*) were the decisive factors in the integration process and that the *A. tumefaciens* Vir proteins encoded on the Ti- plasmid do not play such a role. However, this document does not disclose what these factors may be, nor how they can be influenced. From this, it can be concluded that there is no incentive for the person skilled in the art to combine Jackson with Bundock, and even if they would be combined, they do not disclose the present invention. Applicants further submit that Bundock does not make up for the lack of teachings in Jackson noted *supra*; thus the references, when combined, do not teach each and every element of the claims.

Consequently, applicants respectfully request the withdrawal of the rejections of claims 5,

11, 16, and 21 under 35 U.S.C. § 103(a) and reconsideration of same.

## CONCLUSION

In light of the above amendments and remarks, applicants respectfully request reconsideration of the application. If questions remain after consideration of the foregoing, or if the Office should determine that there are additional issues which might be resolved by a telephone conference, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,

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Enclosures: IDS